REMARKS

Claims 12-16, 19-20 and 24 remain pending in the application. No new matter has been added.

Rejection of Claims 12-16, 19, 20 and 24 Under 35 USC § 103(a)

Claims 12-16, 19, 20 and 24 are rejected as being unpatentable over Kinstler *et al.* (referred to herein as Kinstler). In particular, the Examiner relies on column 19, lines 38-67, of Kinstler as teaching N-terminal derivatization of interferon with polyethylene glycol, and column 11, lines 55-58 and 61 (incorporating by reference Remington's Pharmaceutical Sciences, (1990) 18th Ed pages 1475-1712) as teaching incorporation of interferon derivatives into microcapsules of polylactic acid and polyglycolic acid with a diameter between 1 and 5000 microns. The Examiner concludes that:

> "Those of ordinary skill would have found it well will to conjugate interferons or CSF with polyethylene glycol, and further to microencapsulate said conjugated bioactivities in a biodegradable polymer such as polylactic or polyglycolic acids, and further to expect similar therapeutic results from the use thereof given the teachings of Kinstler et al. The instant invention would have been obvious to one of ordinary skill at the time of invention given the teachings of Kinstler"

Applicants respectfully traverse this rejection for at least the following reasons.

I. Claims 12 and 13 of the of the present invention are drawn to a method for producing microparticles or nanoparticles for controlled release of an interferon, wherein the method includes the step of dissolving a biodegradable polymer and a conjugate of an interferon and a hydrophilic polymer in a solvent ***to form a monophase***.

As pointed out in Applicant's previous response, Kinstler does ***not*** teach or suggest a method for producing microparticles or nanoparticles that involves the step of dissolving a biodegradable polymer and a conjugate of an interferon and a hydrophilic polymer in a solvent to form a monophase, as recited in claims 12 and 13. However, the Examiner has maintained the rejection on the grounds that "Kinstler derivatizes the IFN using a hydrophilic polymer and discusses its homogenous property in col. 9, line 36", which the Examiner asserts "inherently entails a monophase".

Applicants respectfully disagree. Kinstler, in column 9, teaches a homogeneous preparation of interferon-PEG conjugates comprising a single PEG molecule attached to a molecule of interferon i.e., a single species of PEG-interferon. Kinstler does ***not*** teach or suggest a method for dissolving this interferon-PEG conjugate in a solvent ***to form a monophase i.e., a solvent system with a single phase***, as presently claimed.

Nor would the method taught by Kinstler inherently involve formation of a monophase. Indeed, microparticles containing homogeneous preparations of PEG-interferon (i.e., single species of PEG-interferon) can be formed using a variety of methods which do ***not*** necessarily involve forming a monophase (i.e., a solvent system with a single phase), as suggested by the Examiner. For example, the "water/oil/water" emulsion method (described in Examples 2, 3, 8, 9, 14 and 15 of instant application) can produce microparticles containing homogeneous preparations of protein-PEG conjugates. This does ***not*** necessarily involve the step of forming a ***monophase***. In fact, Applicant's were ***first*** to discover that dissolving a PEG-protein conjugate together with a biodegradable polymer in an organic solvent to form a monophase can be used to produce superior microparticle preparations.

Accordingly, for at least the foregoing reasons, the method recited in claims 12 and 13 is non-obvious.

II. Claims 14-16 are drawn to pharmaceutical formulations comprising a ***derivatized biodegradable polymer containing hydrophilic and hydrophobic regions***.

In their previous response, Applicants pointed out that Kinstler fails to teach or suggest ***derivatized biodegradable polymer containing hydrophilic and hydrophobic regions***. However, the Examiner has maintained the rejection by asserting that Kinstler "does include both the hydrophilic area (polyethylene glycol) and the hydrophobic area (polylactic and polyglycolic acids) ***separately***".

Applicants respectfully disagree. Kinstler teaches particular hydrophobic biodegradable polymers, namely polylactic acid and polyglycolic acid, as well as a particular non-biodegradable, hydrophilic polymer, namely PEG. Kinstler does ***not*** teach or suggest a biodegradable polymer ***derivatized to include both hydrophobic and hydrophilic regions on the same molecule***. Indeed, the mere disclosure of separate hydrophilic and hydrophobic polymers does not constitute or render obvious disclosure of a single polymer containing both ***hydrophilic and hydrophobic*** regions let alone a biodegradable polymer that has been ***derivatized***, as

claimed by the Applicants. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness under 35 USC §103 and thus, for at least the foregoing reasons, claims 14-16 are non-obvious.

III. Claims 19, 20 and 24 are drawn to pharmaceutical formulations comprising ***microparticles having a diameter predominantly between 20 and 100 um.***

In their previous response, Applicants pointed out that Kinstler fails to teach or suggest pharmaceutical formulations comprising ***microparticles with a diameter predominantly between 20 and 100 um***. However, in the latest Office Action, the Examiner has maintained the rejection and stated that "the broad recitation" of "tenths of a um to 5000 um....clearly encompasses the claimed particle size".

Applicants respectfully disagree. From the outset, just because the microparticle size range taught by Kinstler encompasses the particular range claimed by the Applicants, does ***not*** necessarily render the claimed range obvious. MPEP 2144.08 states that "the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness".

Indeed, the particular size range (20 to 100 um) claimed in the present application would ***not*** have been obvious in view of the broad range taught by Kinstler. Applicants respectfully point out that the range of particle sizes taught by Kinstler is extremely broad, encompassing more than a ***10,000 fold range*** of sizes. In contrast, the range of particle sizes encompassed by claims 19, 20 and 24 is limited to 20 to 100 um (i.e. a ***5 fold range***).

Moreover, Kinstler fails to provide any guidance whatsoever regarding how to obtain microparticles having a diameter between 20 and 100 um, as claimed. Thus, it would not have been obvious how to generate such microparticles. Indeed, even if the skilled artesan had been motivated to modify the teachings of Kinstler, as suggested by the Examiner, they would not have had any reasonable expectation of success in obtaining microparticles of the claimed size range.

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness under 35 USC §103 and thus, for at least the foregoing reasons, claims 19, 20 and 24 are non-obvious.

In summary, Kinstler fails to render claims 12-16, 19, 20 and 24 obvious under 35 USC §103 and Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Applicants believe that no fee, other than the extension fee and the RCE fee, is due for this Amendment and Response. If another fee is occasioned, the Commissioner is hereby authorized to charge any deficiencies which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. PRJ-006CNRCE2.

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Respectfully submitted,

By

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